REMARKS

Claims 24-27, 36-44, 47, 52 and 55-59 are pending. Claims A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. Applicant respectfully requests further consideration of the present application in light of the following remarks.

Claims 24-26, 36-38, 44, 47, 52, and 55-57 are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and Li *et al.* Claims 24-27, 36-38, 44, 52, and 55-57 are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and United States Patent No. 5,106,955. Claims 24-26, 36-42, 44, 52, and 55-57 are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and United States Patent No. 5,686,072 and PCT publication WO 95/09917. Claims 24-26, 36-39, 44, 52, and 55-57 are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and European Patent Application No. 510949. Claims 24-27, 36-38, 43, 44, 52, and 55-59 and are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and United States Patent No. 5,698,178. Claims 24-27, 38, 43, 44, 52, 55-59 are rejected under 35 U.S.C. §103(a) based on WO 96/04925 in view of Maloney *et al.* and United States Patent No. 5,698,178.

All of these rejections are based on the combination of United States Patent No. 5,789,554 or its equivalent WO96/04925 ("Leung") in view of Maloney *et al.* ("Maloney") with the addition of one or two additional references, and Maloney is the sole reference cited in support of the obviousness of combinations of anti-CD22 immunoconjugates and anti-CD20 naked antibodies. Therefore, once the impropriety of this portion of the rejection is established, all of the rejections based on Leung and Maloney must fall.

Leung describes immunoconjugates of LL2 with cytotoxic agents or labels (see abstract). The examiner admits that Leung does not teach combinations of LL2 with anti-CD20 antibodies as recited in claim 24 and claims dependent thereon, but urges that it would have been obvious to combine anti-CD22 immunoconjugates and naked anti-CD20 antibodies based on the disclosure in Maloney of treating B-cell lymphoma, NHL, and other leukemias and lymphomas with a chimeric anti-CD20 monoclonal antibody, rituximab. She argues that a skilled artisan would have expected a mixture of antibodies to the different epitopes "would be more efficacious in therapeutic methods, as well as enhance the treatment modality," citing the last paragraph on page 2465 of Maloney.

The cited portion of Maloney discloses that "extension of these studies to patients with minimal disease, using antibody alone or in combination with ***conventional therapies***, may provide the greatest benefit. "Conventional therapies" at the time of the Maloney article, circa 1994, were chemotherapies, not antibody therapies. Therefore, the disclosure in Maloney that anti-CD20 may be combined with a "conventional therapy" would not have suggested a combination with anti-CD22 immunoconjugate therapy, as presently claimed. No *prima facie* case of obviousness exists.

Moreover, Maloney *teaches away* from any use of immunoconjugates, and thus is improperly combined with Leung to allege the obviousness of the presently recited combination. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, ***would be discouraged*** from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 31 U.S.P.Q.2d 1130 (Fed. Cir. 1994), emphasis added. More recently, in *Ecolochem, Inc. v. Southern California Edison Company*, 227 F.3d 1361 (Fed.Cir. 2000), cert. den., 121 S.Ct. 1607, the Federal Circuit noted that the combination of two prior art references does not render patent claims obvious if there was no evidence of any suggestion, teaching, or motivation to combine the information from the prior art and where there was evidence that the prior art actually taught away from the patented process. In *Ecolochem*, the prior art taught away from a mixed-bed ion exchange process; therefore, no motivation existed for one of ordinary skill in the art to produce the patented technology.

Similarly, here Maloney teaches away from the use of antibodies that are radiolabeled or conjugated to a cytotoxic agent, noting that:

> The [anti-CD20] antibody preparation is used directly for therapy, not requiring conjugation to drugs, toxins, or radiolabels, each of which requires extensive safety testing and may not be stable after formation of the active conjugate. Antibody modification may interfere with antigen binding… significant hematologic toxicity is associated with the use of high-dose radiolabeled conjugates…In some studies, immunotoxin conjugates have been associated with significant toxicities (page 2585, penultimate paragraph).

Thus, a skilled artisan ***would be discouraged*** from the very combination urged to have been obvious by the examiner. The combination of Leung and Maloney would not have suggested therapy with a combination of an anti-CD22 immunoconjugate and a naked anti-CD20 antibody. No *prima facie* case of obviousness of claim 24 and claims dependent thereon is supportable based upon the combination of a primary reference that teaches the use of immunoconjugates (Leung)

and a secondary reference (Maloney) that teaches the use of naked antibodies and specifically teaches away from any use of immunoconjugates.

In the current action, the examiner commented that "anti-CD22 is regarded as a conventional therapy" and that Maloney notes that "using antibody [CD20] alone or in combination with conventional therapies, may provide the greatest benefit." The examiner cites Webster's Collegiate Dictionary as defining "conventional" as meaning "developed, established, or approved by general usage; customary." She then urges that Leung makes it clear that therapy with anti-CD22 antibody "has been developed and established and is reasonable regarded as a conventional therapy as supported by the definition of 'conventional.'" In this regard, she notes that references directed to anti-CD22 therapies have dates as early as 1991.

Maloney suggests the possible implementation of further studies in which the CD20 antibody is combined with "conventional therapies." If the examiner is urging that all antibody therapy was "conventional" as of 1994, such that a skilled artisan would have been motivated to combine a different antibody, such as an anti-CD22 antibody, in treatment based on Maloney's comment regarding the addition of "conventional therapies" to his anti-CD20 antibody, this is unsupported by anything in the record. Certainly Maloney itself does not support the examiner's statement that treatment with an antibody was "conventional therapy" in 1994. Maloney is a report of results from a ***Phase I clinical trial*** to evaluate the safety of anti-CD20 antibody as a single agent therapeutic. A Phase I trial is the earliest stage in clinical trials of an ***investigational drug*** – and therefore Maloney is antithetical to the examiner's conclusion that treatment with an antibody constituted "conventional therapy." "Conventional" means "conforming to established practice or accepted standards; traditional" (The American Heritage® Dictionary of the English Language: Fourth Edition - 2000). An investigational drug in Phase I clinical trials cannot be considered a conventional therapy, *i.e.*, it does ***not*** conform to established practice or accepted standards." By definition, investigational drugs have not been "accepted." Companies can provide investigational drugs to doctors if they are part of a drug trial covered by an FDA-approved protocol, and such drugs are ***by definition not conventional***, since they are not available for use by any doctor on any patient.

The first approved antibody for therapy of any malignancy was the anti-CD20 antibody rituximab that is the subject of Maloney, but it was not approved until 1997, and therefore there was no cancer therapy with any antibody that was a conventional therapy in 1994, let alone a combination therapy with multiple antibodies. Even today, after the advantage of epratuzumab

combined with rituximab has been published, this combination has not been approved and hence is ***not*** conventional therapy. In fact, ***no antibody combination has ever been approved***.

Current reviews and texts support the fact that combination antibody therapy is not conventional. Some articles began to discuss the possibility of such combination therapies following applicant's publication of their studies of epratuzumab and rituximab in about 2002/2003, but none indicate that such therapy is "conventional." The following articles show that antibody therapy generally, and combination antibody therapy in particular is not considered "conventional" in the art, even today:

- Hiddemann in 1995 states that "more experimental approaches consist of the application of immunotoxins or radioisotopes, coupled to monoclonal antibodies directed against lymphoma-specific antigen" for the treatment of NHL, *i.e.*, even single antibody therapy was considered an "experimental approach and not a conventional therapy. *Eur. J. Cancer*, 31A(13-14):2141-5 (1995).

- Skarin *et al.* in 1997 alludes to "the use of specific monoclonal antibodies directed against cell surface antigens has contributed to the understanding of [NHL]." That is, the antibodies were considered useful in understanding NHL, but not in therapy. With respect to therapy, Skarin *et al.* list "combination chemotherapy without or without regional radiotherapy." *CA Cancer J. Clin.*, 47(6):351-72 (1997).

- An educational review published in 1998 notes under the heading "Monoclonal Antibodies" that:

  > New treatment approaches for low-grade lymphoma include monoclonal antibodies that attach to receptors found on B-lymphocytes. One general approach uses radiolabeled antibodies; another uses a "naked" antibody. *Preliminary studies of these monoclonal antibodies as single agents* has demonstrated encouraging response rates and some evidence of long-term disease control, but the median duration of response and impact on overall survival are still unknown.
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  > Webster *et al.*, *Oncology*, 12(5):697-714 (1998) -- emphasis added.

- In 1999, Czuczman *et al.* showed that a combination treatment of anti-CD20 monoclonal antibody and CHOP chemotherapy (a "conventional therapy") showed improved efficacy. This is a treatment of anti-CD20 antibody and conventional

therapy as mentioned in Maloney, but does not suggest combination antibody therapy. *Journal of Clinical Oncology*, 17:268, (1999).

- In an article about the current therapeutic paradigm for the treatment of NHL, Fisher in 2000 noted that patients with indolent NHL may be treated with single-agent alkylating agents, radiation therapy, or combination chemotherapy, while indicating that none of these approaches have produced curative results. Fisher notes the need for "innovative treatment strategies," and mentions the use of interferon, monoclonal antibodies with or without radioisotopes, purine analogues, and even high-dose therapy with stem-cell rescue are under investigation. Thus, in 2000, each of these was still considered investigational, and combinations of antibodies are not suggested. *Semin Oncol.* Dec; 27(6 Suppl 12):2-8 (2000).

- "What is New in Lymphoma," published in 2004, cites rituximab as an advancement in the treatment of NHL. Efforts to improve the activity of rituximab are noted, and include increasing the number of weekly infusions, delivering higher doses and increasing dose density. Combinations with CHOP are also mentioned. A Phase II study of a combination of rituximab with epratuzumab reported in 2003 and a phase I/II study of the combination of galizimab are mentioned, demonstrating that combination antibody therapy was still very much investigational at this later date. Cheson, *CA Cancer J Clin.* Sep-Oct; 54(5):260-72 (2004)

- The 2003 Merck Manual lists "many new treatments … for indolent lymphomas. These include monoclonal antibodies, which bind to lymphoma cells and kill them. These antibodies (immunoglobulins), such as rituximab, are given intravenously. Sometimes, the monoclonal antibodies are modified so that they can carry radioactive particles or toxic chemicals directly to the cancer cells in different parts of the body. It remains uncertain whether these monoclonal antibodies can cure non-Hodgkin's lymphomas, or if they can achieve better results when combined with chemotherapy. Combinations with other antibodies are not included in the list of conventional or new therapies.

Indeed, even later articles published by IDEC fail to suggest combinations of their anti-CD20 antibody with other antibodies. In 2001, they published "Non-Hodgkin's lymphoma: review of conventional treatments" (*Curr Pharm Biotechnol.*, 2(4):279-91 (2001)), which states that:

> Conventional treatment for patients with newly-diagnosed non-Hodgkin's lymphoma (NHL) includes radiation or chemotherapy. In addition, those with asymptomatic low-grade disease may follow a "watch and wait" approach. Single agent oral alkylating therapy and CVP (cyclophosphamide, vincristine, and prednisone) have become a mainstay of treatment for low-grade NHL. High intensity chemotherapy consisting of the anthracycline, doxorubicin along with cyclophosphamide, vincristine and prednisone (CHOP) is offered as standard treatment for intermediate-grade NHL… Novel approaches to treatment are therefore needed. Monoclonal antibodies may fulfill this need, administered either as single agents or in conjunction with conventional cytotoxic approaches.

And in 2000, Maloney himself published "Monoclonal antibodies in lymphoid neoplasia: principles for optimal combined therapy," (*Semin Hematol*, 37(4 Suppl 7):17-26 (2000)), which speaks of the possibility of trying "novel combinations" and suggests that randomized, prospective trials are required to determine clinical utility. Thus, statements in later IDEC articles, including one by Maloney, contravene the examiner's position that Maloney's mention in 1994 of a combination of anti-CD20 antibody with "conventional therapies" would encompass combination antibody therapy as presently claimed.

Applicant now provides further evidence, in the form of Declarations under 37 CFR §1.132 by three well-known experts in the field of antibody therapy. These declarations confirm applicant's previous assertions that antibody therapies were not "conventional" in 1994, when Maloney published the cited article.

Dr. Kenneth Foon is the Director of Clinical Investigation and Program Director for the Leukemia and Lymphoma Program at the University of Pittsburgh Cancer Institute. He has an extensive background in the field of immunotherapy for cancer treatment, and has been the principal investigator on clinical trials relating to immunotherapy of various B-cell malignancies, including a current Phase II clinical trial to study effects of a combination of rituximab, fludarabine and cyclophosphamide on patients with previously untreated chronic lymphocytic leukemia. Dr. Foon attests that "conventional therapies" at the time of the Maloney article, circa 1994, were chemotherapies, not antibody therapies. He further notes that the first approved antibody for therapy of any malignancy was the anti-CD20 antibody rituximab that is the subject of Maloney, but that it was not approved until 1997, and therefore there was no cancer therapy with any antibody that was a conventional therapy in 1994. Thus, he attests that the disclosure in Maloney that anti-CD20 may be combined with a "conventional therapy" would not have suggested to him therapy with a combination of an anti-CD20 antibody and another antibody, such as an anti-CD22 antibody.

He cites his current clinical trial which is referenced in paragraph 1 of his declaration as an example of a combination of anti-CD20 (rituximab) therapy with a conventional drug therapy (fludarabine and cyclophosphamide), such as is envisioned by Maloney 1994. Dr. Foon further declares that treatment with anti-CD22 antibody also was not conventional circa 1994, and notes that Goldenberg *et al.*, *J. Clin. Oncol.*, 9: 548-564 (1991) provided results from a pilot Phase I study involving a small number of patients to see the feasibility of giving this radiolabeled antibody, involving targeting tumor and organs, doses delivered to tumor and normal organs, and any evidence of efficacy in a small number of patients, and does not establish that treatment with anti-CD22 antibody was "conventional." He cites the Cheson article, which references 2003 reports of both a Phase II study of a combination of rituximab with epratuzumab and a phase I/II study of the combination of galiximab and rituximab, as demonstrating that combination antibody therapy was still very much investigational at this later date.

Dr. Leonard is the Clinical Director at the Cornell Center for Lymphoma and Myeloma at the New York-Presbyterian Hospital. He also has an extensive background in the field of immunotherapy for cancer treatment. He has been a key investigator on clinical trials relating to immunotherapy of various B-cell malignancies, particularly with rituximab. Currently he is the principal investigator for a phase II trial that is studying rituximab versus lenalidomide versus rituximab + lenalidomide in recurrent follicular Non-Hodgkin Lymphoma (NHL) after relapse from a rituximab-containing combination regimen. Dr. Leonard agrees with Dr. Foon that "conventional therapies" at the time of the Maloney article, circa 1994, were chemotherapies, not antibody therapies, and that the first approved antibody for therapy of any malignancy was the anti-CD20 antibody rituximab (the subject of Maloney) which was not approved until 1997. Thus, he attests that there was no cancer therapy with any antibody that was a conventional therapy in 1994, and that the disclosure in Maloney that anti-CD20 may be combined with a "conventional therapy" would not have suggested to him therapy with a combination of an anti-CD20 antibody and another antibody, such as an anti-CD22 antibody. In this regard, he mentions that he currently is the principal investigator of a phase II study of combination antibody therapy, in this case rituximab plus galiximab (anti-CD80) (currently in press for publication in *Annals of Oncology*), but confirms that he would not have understood Maloney 1994 to have suggested such a combination antibody therapy based on the statement in the article that "extension of these studies to patients with minimal disease, using antibody alone or in combination with ***conventional therapies***, may provide the greatest benefit." Rather, he would have understood Maloney's statement to suggest combinations of the anti-CD20 antibody with chemotherapy, which was "conventional" in 1994. This is so

because even single antibody therapy was not conventional in 1994. He echoes Dr. Foon's citation of the Cheson article, as demonstrating that combination antibody therapy was still very much investigational circa 2003.

Dr. Czuczman is an Associate Professor of Medicine at the Roswell Park Cancer Institute, Buffalo, New York, and also has an extensive background in the field of immunotherapy for cancer treatment. He has been a key investigator on clinical trials relating to immunotherapy of various B-cell malignancies, particularly with rituximab. Currently he is the principal investigator for a Phase II trial studying the effects of giving rituximab together with liposomal doxorubicin to patients with relapsed or refractory B-cell non-Hodgkin's lymphoma, and also for a Phase III Trial of CHOP plus rituximab versus CHOP plus iodine-131-labeled monoclonal anti-B1 antibody (tositumomab) for treatment of newly diagnosed follicular Non-Hodgkin's Lymphomas. He also is the principal investigator for a phase II trial studying of the effects of administering rituximab together with galiximab to patients with stage II, stage III, or stage IV non-Hodgkin's lymphoma. Dr. Czuczman attests that the disclosure in Maloney that anti-CD20 may be combined with a "conventional therapy" would not have suggested to him therapy with a combination of an anti-CD20 antibody and another antibody, such as an anti-CD22 antibody, because "conventional therapies" at the time of the Maloney article, circa 1994, were chemotherapies, not antibody therapies. He notes that two of his current clinical trials referenced in paragraph 1 of his declaration relate to combinations of the anti-CD20 antibody rituximab with a conventional drug therapy (liposomal doxorubicin or CHOP) along the lines envisioned by Maloney 1994.

Dr. Czuczman published a report in 1999, previously discussed by applicants, which showed that a combination treatment of anti-CD20 monoclonal antibody and CHOP chemotherapy (a "conventional therapy") showed improved efficacy. Czuczman *et al.*, *Journal of Clinical Oncology*, 17:268, (1999). He cites this as a treatment of anti-CD20 antibody and conventional therapy as mentioned in Maloney, and states that it also does not suggest combination antibody therapy. He also cites the Cheson article as demonstrating that combination antibody therapy was still very much investigational circa 2003.

Claims 24-27, 36-44, 47, 52, and 55-89 are provisionally rejected under the doctrine of obviousness-type double patenting over claims 24-44 of co-pending application No. 10/314,330. The examiner states that applicant's request has been considered but found unpersuasive and the rejection is maintained. Applicant did not request that the rejection be withdrawn, but merely that it be held in abeyance until such time as allowable subject matter is indicated in one of the two

applications. Until such time, the rejection is "provisional" and is indicated as such in the Official Action. According to MPEP 822.01:

> The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications. If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.

Thus, no further action on applicant's part with respect to the provisional double patenting rejection is required. Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

If there are any problems with this response, Applicant's attorney would appreciate a telephone call. In view of the foregoing, it is believed none of the references, taken singly or in combination, disclose the claimed invention. Accordingly, this application is believed to be in condition for allowance, the notice of which is respectfully requested.

Respectfully submitted,

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